SUPPORTING MATERIALS

A Microscale Heck Reaction In Water

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The information contained within this document is organized into three sections-

1. **Laboratory Notes For Students** – background information and industrial relevance of the Heck reaction, hazards and safety, experimental procedures and post-lab questions (pages 2 - 7).

2. **Additional Notes For Instructors** – equipment needs, synthetic notes, a detailed reaction mechanism and required chemicals with CAS numbers (pages 8 - 10).

3. **Spectroscopic Information & Physical Data** – (E)-4-acetyl cinnamic acid product $^1$H NMR, $^{13}$C NMR, MS and IR spectra and assignments (pages 11 - 15).
Laboratory Notes For Students

*Estimated Length Of Experiment:* 3 hours

**Experimental Objectives**

1. To synthesize a stereoisomer of 4-acetylcinnamic acid by a Heck reaction.
2. To characterize the reaction product by $^1$H NMR, $^{13}$C NMR and IR spectroscopy.
3. To deduce and rationalize the product geometry via $^1$H NMR spectroscopy.
4. To appreciate the advantages of using water as the solvent for this (and other) organic reactions.

**Background**

The Heck reaction is a very popular approach for synthesis of $\alpha,\beta$-unsaturated carbonyl compounds (1). This method typically involves reacting an electron-deficient alkene with an aromatic halide in the presence of a palladium (0) catalyst under basic conditions (below).

$$
\text{Ar} - X + \text{EWG} \rightarrow \text{Ar} - \text{EWG} + HX
$$

* $X = \text{Br, I}$
* $\text{EWG} = \text{electron-withdrawing group}$

**A Generalized Heck Reaction**

Many important steps involved in the preparation of fine chemicals are accomplished by Heck reactions (2). Examples include the synthesis of 2-ethylhexyl $p$-methoxycinnamate, a popular sunscreen component, and the preparation of L 699,392 and Singulair™ (anti-asthma drugs).
Heck Synthesis Of Anti-Asthma Drugs
These examples illustrate that Heck reactions are typically undertaken in an organic solvent such as acetonitrile or N-methyl-2-pyrrolidone. In addition, an organic base is regularly utilized (e.g. triethylamine) (3). There currently exists much lively research in the field of “green chemistry” – that is, designing synthetic reaction conditions that are less deleterious to the environment than previous methodologies. One approach is to replace popular reaction solvents with more environmentally benign alternatives such as ionic liquids or fluorous ethers (4). Although many organometallic reactions (e.g. the Grignard reaction) do not lend themselves to aqueous conditions, it is possible to exploit water as a viable solvent for certain transformations. This is particularly important for reactions creating new carbon-carbon σ-bonds as these form the basis of organic synthesis (5). Today’s reaction illustrates the advances made in improving the “greenness” of an industrially important synthetic method. Acrylic acid (propenoic acid) is employed as a particularly reactive alkene and palladium (II) chloride used as the catalyst (6). These conditions afford mild and facile preparation of cinnamic acid derivatives (note that Pd (II) must be reduced to Pd (0) in order to generate the active catalytic species).

\[
\text{Iodoacetophenone} + \text{Acrylic acid} \xrightarrow{\text{PdCl}_2, \text{Na}_2\text{CO}_3, \text{H}_2\text{O}} \text{Cinnamic acid}
\]

\( (Z) \) or \( (E) \) ?

**Aqueous Heck Synthesis Of A Cinnamic Acid**

**Safety Notes**

Wear eye protection, a laboratory coat and protective gloves during this experiment. 4-Iodoacetophenone and cesium carbonate are irritating to the eyes, respiratory system and skin. Acrylic acid is flammable and harmful to the eyes, respiratory system and skin. Palladium (II) chloride is irritating to the respiratory system and skin and may cause sensitization by skin contact. Methanol is highly flammable and toxic if swallowed. Hydrochloric acid causes burns and is irritating to the respiratory system.

**CAUTION – PERFORM ALL SYNTHETIC AND PURIFICATION OPERATIONS IN A FUMEOOD**
Experimental Procedure

A table of the reactant/solvent physical properties is detailed below:

<table>
<thead>
<tr>
<th>Compound</th>
<th>GMW</th>
<th>Amount Added</th>
<th>mmol</th>
<th>mp (°C)</th>
<th>bp (°C)</th>
<th>d (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-iodoacetophenone</td>
<td>246.05</td>
<td>246 mg</td>
<td>1.00</td>
<td>82-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sodium carbonate</td>
<td>105.99</td>
<td>318 mg</td>
<td>3.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acrylic acid</td>
<td>72.06</td>
<td>100 μL</td>
<td>1.46</td>
<td>12-15</td>
<td>1.05</td>
<td></td>
</tr>
<tr>
<td>palladium (II) chloride</td>
<td>177.33</td>
<td>1.8 mg</td>
<td>0.0101</td>
<td>678-680</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1 M HCl</td>
<td>36.46</td>
<td>-98</td>
<td>64</td>
<td>0.791</td>
<td></td>
<td></td>
</tr>
<tr>
<td>methanol</td>
<td>32.04</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. **IN A FUMEHOOD**, place the following in a 25 mL round bottomed flask: 4-iodoacetophenone (246 mg); sodium carbonate (318 mg); acrylic acid (100 μL, measured with an automatic delivery pipette); and water (5 mL – automatic delivery pipette). Add a magnetic stir bar.

2. Add water (~ 1 mL) to the supplied vial containing palladium (II) chloride (1.8 mg) to create a suspension. Transfer the suspension to the reaction mixture and use water (~ 1 mL) to rinse in any PdCl₂ not initially added.

3. Heat the mixture **vigorously** under reflux (water condenser) for 60 – 75 minutes (can be continued for longer), using a sand bath as the heat source and maintaining rapid stirring.

4. Remove the flask from the sand bath and allow cooling to room temperature. Once cool, remove the catalyst by gravity filtration.

5. Add aqueous HCl (1 M) to the filtrate until acidic to litmus paper, causing a precipitate to form. Collect the solid by vacuum filtration.

6. Recrystallize the crude product using 50:50 methanol:water as solvent. Allow the solution to cool slowly to room temperature and then cool in an ice-bath.

7. Collect the purified compound by vacuum filtration (using a Hirsch funnel) and dry thoroughly. Remove the solid from the funnel, weigh and calculate the percentage yield. Take appropriate physical measurements (mp, IR, ¹H, ¹³C NMR spectra) and identify whether you have synthesized the (Z)- or (E)-stereoisomer of 4-acetylcinnamic acid.

**SUBMIT A SAMPLE OF YOUR SYNTHESIZED PRODUCT WITH YOUR REPORT**
Clean-Up

Dispose of all waste into the appropriately marked containers in the fumehoods. Dismantle and clean all glassware with soap and water.

Laboratory Report

Your report should contain the following aspects:

1. Discussion of the Heck reaction performed, including
   (i) a detailed “curved-arrow” reaction mechanism for formation of 4-acetylchinnamic acid, focusing on the operative catalytic cycle. Points to include:
      a) in situ reduction of Pd (II) to Pd (0)
      b) alkene insertion
      c) elimination and alkene C=C formation
      d) reductive elimination and regeneration of Pd (0)
   (ii) the calculated percent yield, with reference to similar experiments (3)
   (iii) identification of product alkene geometry, based on the $^1$H NMR spectrum (see below) and reaction mechanism – explain why the Heck reaction is stereoselective (and regioselective).

2. Discussion of spectral data obtained, including
   (i) an IR spectrum analysis (in terms of product absorbances and similarities/differences from the IR spectra of 4-iodoacetophenone and acrylic acid)
   (ii) an interpretation of the $^1$H NMR of 4-acetylchinnamic acid (with respect to chemical shifts, spin-spin splitting patterns and coupling constants ($J$ values)). Can you confirm the product alkene geometry from this spectrum? How?

3. An outline of the benefits of performing the Heck reaction under aqueous conditions (compare and contrast this reaction with the approach in reference (3), and original reports of the Heck reaction). Why is it important to develop reactions that use water as the solvent?
Useful References


Additional Notes For Instructors

Equipment Needs

1 x 25 mL round bottomed flask
1 x 25 mL Erlenmeyer flask
1 x 50 mL Erlenmeyer flask
Magnetic stirrer/hotplate
Magnetic stir bar
Sand bath
Reflux condenser
Glass funnel/filter paper for gravity filtration
Hirsch funnel and flask for vacuum filtration
Ice bath
3 x Pasteur pipettes
Automatic delivery pipette (set to 5.0 mL, can be shared)
Automatic delivery pipette (set to 100 µL, can be shared)

Notes Regarding Synthesis Of (E)-4-Acetylcinnamic acid & Related Compounds

1. The protocol outlined for synthesizing this compound assumes that the product alkene geometry is unknown – this adds an instructive investigative feature to the experiment.

2. Student yields for this reaction typically range between 53 – 74% after one recrystallization of the crude product from aqueous methanol. A typical recrystallization requires 15 – 20 mL of 50:50 methanol:water. If the crude product has not completely dissolved after addition of 20 mL hot solvent, it is advisable to add hot methanol to effect dissolution.

3. It is possible to use potassium carbonate or cesium carbonate as the base instead of sodium carbonate. Using cesium carbonate leads to product yields of up to 80%.

4. The reaction works as described to generate other cinnamic acid derivatives under the stated conditions, although sometimes in a lower yield. Examples:

<table>
<thead>
<tr>
<th>Aromatic Halide</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Bromobenzaldehyde</td>
<td>4-Formylcinnamic acid</td>
<td>67%</td>
</tr>
<tr>
<td>Iodobenzene</td>
<td>Cinnamic acid</td>
<td>35%</td>
</tr>
<tr>
<td>4-Bromoanitrobenzene</td>
<td>4-Nitrocinnamic acid</td>
<td>36%</td>
</tr>
<tr>
<td>4-Iodoanisole</td>
<td>4-Methoxycinnamic acid</td>
<td>39%</td>
</tr>
</tbody>
</table>
**Reaction Mechanism**

**Pre-catalyst activation**

![Pre-catalyst activation diagram]

**Catalytic cycle**

![Catalytic cycle diagram]

**Product isolation**

![Product isolation diagram]
Stereoselectivity of syn β-hydride elimination

Chemicals Required & CAS Numbers

<table>
<thead>
<tr>
<th>Chemical</th>
<th>CAS Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Iodoacetophenone</td>
<td>13329-40-3</td>
</tr>
<tr>
<td>Acrylic acid (propenoic acid)</td>
<td>79-10-7</td>
</tr>
<tr>
<td>Palladium (II) chloride</td>
<td>7647-10-1</td>
</tr>
<tr>
<td>Sodium carbonate</td>
<td>497-19-8</td>
</tr>
<tr>
<td>Aqueous hydrochloric acid</td>
<td>7647-01-0</td>
</tr>
<tr>
<td>Methanol</td>
<td>67-56-1</td>
</tr>
<tr>
<td>Water</td>
<td>7732-18-5</td>
</tr>
</tbody>
</table>

Ar = $\text{p-C}_6\text{H}_4\text{COCH}_3$
Spectroscopic Information & Physical Data

$^1$H NMR assignments for ($E$)-4-acetylcinnamic acid

![Chemical Structure Image]

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.56</td>
<td>6</td>
</tr>
<tr>
<td>7.96</td>
<td>2 (d, $J = 8.0$ Hz)</td>
</tr>
<tr>
<td>7.82</td>
<td>3 (d, $J = 8.2$ Hz)</td>
</tr>
<tr>
<td>7.64</td>
<td>4 (d, $J = 16.0$ Hz)</td>
</tr>
<tr>
<td>6.66</td>
<td>5 (d, $J = 16.0$ Hz)</td>
</tr>
<tr>
<td>2.59</td>
<td>1</td>
</tr>
<tr>
<td>2.49</td>
<td>DMSO</td>
</tr>
</tbody>
</table>

$^{13}$C NMR assignments for ($E$)-4-acetylcinnamic acid

![Chemical Structure Image]

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>Assignment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>197.4</td>
<td>2</td>
</tr>
<tr>
<td>167.3</td>
<td>9</td>
</tr>
<tr>
<td>142.5</td>
<td>7</td>
</tr>
<tr>
<td>138.6</td>
<td>6</td>
</tr>
<tr>
<td>137.6</td>
<td>3</td>
</tr>
<tr>
<td>128.6</td>
<td>4 or 5</td>
</tr>
<tr>
<td>128.4</td>
<td>4 or 5</td>
</tr>
<tr>
<td>121.8</td>
<td>8</td>
</tr>
<tr>
<td>39.5</td>
<td>DMSO</td>
</tr>
<tr>
<td>26.8</td>
<td>1</td>
</tr>
</tbody>
</table>

$^1$H NMR (400 MHz) of (E)-4-acetylaminic acid (DMSO-$d_6$)
\(^{13}\text{C} \) NMR (400 MHz) of (E)-4-acetylcinnamic acid (DMSO-\textit{d}_6)
Mass spectrum (electron impact) of (E)-4-acetyl-cinnamic acid
Infra-red spectrum of (E)-4-acetylcinnamic acid (Nujol mull)